Statistical Analysis Plan

Study	A Phase 2/3 Multicenter, Randomized, Double-masked, Parallel-group, Placebo-controlled Study to Investigate the Safety, Pharmacokinetics, Tolerability, and Efficacy of ALK-001 in Geographic Atrophy Secondary to Age-related Macular Degeneration
Study Drug Code Name	ALK-001
Study Drug Compound	C20-D3-Retinyl Acetate, or C20-D3-Vitamin A Acetate
USAN/INN Name	Gildeuretinol acetate
Intended Indication	Geographic Atrophy Secondary to Age-related Macular Degeneration (SNOMED: 414875008)
Protocol	ALK001-P3001 (NCT03845582)
IND	108,353
Sponsor	Alkeus Pharmaceuticals, Inc. 44 Brattle Street, 2nd floor Cambridge, MA 02138
Date	20Jun2024
Version	Final v1.0 based on protocol version 1.1 (02/01/2019)

Approval Signatures

The signatures below indicate approval of this Statistical Analysis Plan.

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AF	Autofluorescence
ALK-001	Gildeuretinol acetate or C20-D3-retinyl acetate: the investigational drug assessed in this study
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AMD	Age-related Macular Degeneration
AST	Aspartate Transaminase
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index
BQL	Below Quantification Limit
CFP	Color Fundus Photograph
CI	Confidence Interval
CNV	Choroidal Neo Vascularization
CSR	Clinical Study Report
DBL	Database Lock
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
EVA	Electronic-ETDRS Visual Acuity
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FAS	Full Analysis Set
FRI	Functional Reading Independence Index
GA	Geographic Atrophy
HCT	Hematocrit
HDL	High-density Lipoprotein
HGB	Hemoglobin
INN	International Nonproprietary Names
IOP	Intraocular Pressure
IReST	International Reading Speed Test
ITT	Intent to Treat
LDL	Low-density Lipoprotein
LLD	Low Luminance Deficit
LLOQ	Lower Limit of Quantification
LLVA	Low Luminance Visual Acuity
LMEM	Linear Mixed-Effects Model

LS	Least Squares
MCH	Mean Corpuscular Hemoglobin
MCMC	Markov-Chain Monte-Carlo
MCV	Mean Corpuscular Volume
MAR	Missing at Random
MM	Multi-Modal Assessment
MMRM	Mixed Model for Repeat Measures
MNAR	Missing Not at Random
MNREAD	Minnesota low vision reading chart
MOP	Manual of Performance
MRS	Maximum Reading Speed
OCT	Optical Coherence Tomography
PI	Principal Investigator
PK	Pharmacokinetics
PLT	Platelets
PP	Per Protocol
PT	Preferred Term
QTc	Corrected QT Interval
RBC	Red Blood Cell count
RPD	Reticular Pseudo Drusen
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TTO	Time Trade-Off
USAN	United Stated Adopted Names
VA	Visual Acuity
VFQ-25	Visual Function Questionnaire 25
WBC	White Blood Cell count
wpm	Words per Minute

1.0. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methodology and data handling for the study ALK001-P3001, A Phase 2/3 Multicenter, Randomized, Double-masked, Parallel-group, Placebo-controlled Study to Investigate the Safety, Pharmacokinetics, Tolerability, and Efficacy of ALK-001 in Geographic Atrophy (GA) Secondary to Age-related Macular Degeneration (AMD). This SAP is based on protocol ALK001-P3001 version 1.1, dated 01Feb2019. This SAP was prepared prior to database lock and unmasking. Any deviations from this SAP will be documented in the Clinical Study Report (CSR).

The trial consists of a treatment period of 24 months and is designed to obtain evidence on the effects of gildeuretinol acetate, also named "ALK-001" in this plan, on the mean rate of growth (slope) estimated based on GA area and measured on fundus autofluorescence (FAF) imaging.

The following guidelines were used as a guide to write this plan:

- ICH E3 structure and content of clinical study reports
- ICH E9 statistical principles for clinical trials
- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

2.0. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1 Primary Objective

- To assess the effects of ALK-001 on the growth rate of GA area after 24 months of treatment in subjects with GA secondary to AMD.

2.1.2 Key Secondary Objectives

To evaluate the effects of ALK-001 compared to placebo in subjects with GA secondary to AMD with respect to:

- Low luminance visual acuity (LLVA) score
- Best-corrected visual acuity (BCVA) score

2.1.3 Secondary Objectives

To evaluate the effects of ALK-001 compared to placebo in subjects with GA secondary to AMD with respect to:

- The growth rate of GA lesion(s) between baseline and Month 12
- The growth rate of GA lesion(s) between Month 12 and Month 24
- The growth rate of GA lesion(s) between Month 6 and Month 24
- Low luminance deficit (LLD) score

- Maximum reading speed, as measured by Minnesota Reading (MNRead)
- Binocular reading speed, as measured by International Reading Speed Test (IReST)
- Functional Reading Independence (FRI) Index score
- Visual Functioning Questionnaire 25 Item Version (VFQ-25)
- Incidence of CNV in eyes with GA, when the fellow eye has CNV at baseline

2.1.4 Safety and Pharmacokinetics Objectives

- To assess the safety and tolerability of ALK-001
- To assess the pharmacokinetics of ALK-001

2.1.5 Exploratory Objectives

To evaluate the effects of ALK-001 compared to placebo in subjects with GA secondary to AMD with respect to:

- Retinal function
- Incidence of CNV in eyes with GA, when the fellow eye has intermediate AMD at baseline
- Incidence of advanced AMD (CNV or GA) in the fellow eye, when the fellow eye has intermediate AMD at baseline

2.2. Endpoints

2.2.1 Primary Efficacy Endpoint

- Growth rate of the total area of GA lesion(s) between baseline and Month 24, as measured on fundus autofluorescence (FAF)

2.2.2 Key Secondary Efficacy Endpoints

The key secondary endpoints include:

- Change from baseline in LLVA score at Month 24 as assessed by either Early Treatment Diabetic Retinopathy Study (ETDRS) chart, or an Electronic-ETDRS Visual Acuity (EVA) system (number of letters)
- Change from baseline in BCVA score at Month 24 as assessed by either ETDRS chart or an EVA system (number of letters)

2.2.3 Secondary Efficacy Endpoints

- Growth rate of the total area of GA lesion(s) between baseline and Month 12
- Growth rate of the total area of GA lesion(s) between Month 12 and Month 24
- Growth rate of the total area of GA lesion(s) between Month 6 and Month 24

- Change from baseline in LLD score
- Change from baseline in maximum reading speed at Month 24, as measured by MNRead (wpm)
- Change from baseline in binocular reading speed, as measured by IReST
- Change from baseline in FRI Index score at Month 24
- Change from baseline in VFQ-25 total score
- Incidence of CNV in the study eye, when the fellow eye has CNV at baseline

2.2.4 Safety and Pharmacokinetics Endpoints

- Adverse events (AEs), including serious adverse events (SAEs)
- Laboratory tests (hematology, biochemistry, lipids)
- Vital signs
- 12-lead electrocardiography (ECG)
- Physical examination
- Ocular exam and intraocular pressure (IOP)
- Pharmacokinetics: absolute concentration and percentage of deuterated vitamin A in plasma

2.2.5 Exploratory Endpoints

- Changes in retinal sensitivity, as measured by fundus-tracking microperimetry (Nidek MP1)
- Incidence of CNV in the study eye, when the fellow eye has intermediate AMD at baseline
- Incidence of advanced AMD (CNV or GA) in the fellow eye, when the fellow eye has intermediate AMD at baseline

3.0. STUDY DESIGN

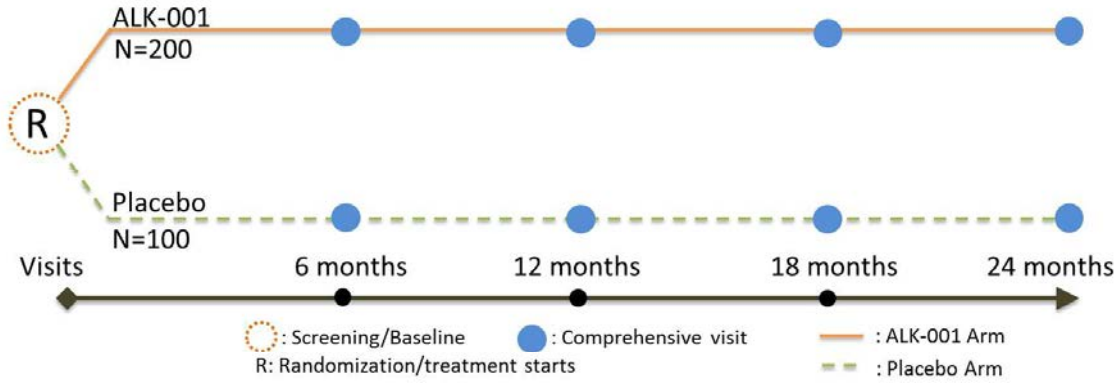
3.1. Overall Study Design

This is a randomized, double-masked, parallel-group, multicenter study evaluating the safety and efficacy of ALK-001 in subjects with GA secondary to AMD.

Approximately 300 subjects were planned to be randomized in a 2:1 ratio to receive either ALK-001 at 14 mg/day or placebo daily for a total treatment duration of 24 months. There was no stratification for randomization, and subjects were randomized using random permuted blocks of size 3 and 6. Due to enrollment delays caused by COVID-19, 200 subjects were randomized with the same 2:1 randomization. Subjects, investigators and study staff, and sponsor staff who may be in contact with investigators or subjects, are masked until after this SAP is submitted to FDA and database lock has occurred.

After an initial screening day (V01), subjects are given a placebo to take once a day during a run-in period. The placebo is indistinguishable from ALK-001, and subjects are unaware that they are receiving the placebo. The run-in period typically lasts between 2 and 4 weeks. At the conclusion of the screening and run-in period, subjects who meet all eligibility criteria were randomized on Day 1 (V02).

Following randomization at V02, subjects have follow-up visits scheduled at Month 6 (V04), Month 12 (V06), Month 18 (V08), and Month 24 (V10) after starting treatment on Day 1. Treatment discontinues at Month 24 (V10). A diagram of the study design and timelines is provided below.



The follow-up visits encompass various assessments. Safety and tolerability will be assessed by monitoring AEs, clinical laboratory tests (biochemistry, hematology, lipids), vital signs, ECG, physical examinations, and pharmacokinetics. Efficacy assessments include GA area measured on FAF imaging, BCVA, LLVA, reading speed, VFQ-25, FRI, microperimetry (optionally performed at sites where available), etc. (Refer to Appendix 1 for a full list of assessments and visit schedule).

Each subject's study duration is up to 2 years and 4 weeks, including screening and run-in period and the 2-year treatment. The study will end when the last subject completes Visit V10 (Month 24) or discontinues the study.

Following completion of the initial treatment period of 2 years, subjects may be given the choice to enter a two-year open-label extension study, which is not covered in this SAP.

3.2. Sample Size

The initial sample size was based on literature data on the progression of GA at the time the study was started. With 300 subjects and assuming that 80% of subjects are evaluable for the primary outcome measure, the study has an 80% power to detect, after 24 months of treatment, a 33% slowing in GA growth rate with a 2-tailed significance of 0.05, assuming a conservative standard deviation of 1.5 mm^2/year and an average GA growth rate of 1.8 mm^2/year in the control group.

Based upon natural history literature data updated as of the date of this SAP, and the area of GA, indicating an average GA growth rate of 1.8 mm^2/year with a standard deviation of 1.2 mm^2/year, with 200 subjects and considering that 80% of subjects completed the study and are expected to

have evaluable data for the primary outcome measure, the study has an 80% power to detect, after 24 months of treatment, a 33% slowing in GA growth rate with a 2-tailed significance of 0.05.

3.3. Study Treatment and Rationale

The study treatment is gildeuretinol acetate (ALK-001, C20-D3-retinyl acetate), a chemically modified vitamin A designed as a replacement for natural vitamin A. ALK-001 has been modified specifically to slow down the formation of toxic vitamin A dimers in the eye while not impairing the visual cycle. Because of its chemical structure, ALK-001 is expected to behave identically to natural vitamin A and to have the same pharmacokinetics and ADME profiles as natural vitamin A. As such, similarly to supplementation with natural vitamin A, ALK-001 will be administered orally at 14 mg/day.

Vitamin A dimers have been implicated in the pathogenesis of AMD because of their toxicity to retinal cells, and as they form and accumulate in the retina with age. The study overall hypothesis is to assess the extent to which slowing vitamin A dimerization by replacing vitamin A with gildeuretinol slows the progression of the growth of GA lesions.

4.0. STATISTICAL ANALYSIS CONVENTIONS AND DEFINITIONS

4.1. Reporting Conventions

Individual subject data obtained from electronic case report forms (eCRFs), external sources, and any derived data will be presented in data listings by subject.

Continuous measures will be summarized by number of observations, minimum, first quartile (Q1), median, mean, third quartile (Q3), maximum, and standard deviation (SD). The minimum and maximum will be presented at the same level of precision (decimal point) of the measurements. Median, Q1 and Q3, and mean will be presented at one greater level of precision (decimal point) as the measurements. SD will be presented at two greater levels of precision. In general, the number of decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided with the same decimal places as the point estimate, unless otherwise specified, in the tables and listings.

Categorical (including binary) measures will be summarized by count and percent. Categories for which counts are 0 will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to “lost to follow-up”, this reason will be included in the table with a count of 0. A row denoted as “Missing” will be included in the count tabulations where necessary to account for dropouts or missing values. Percentages will be rounded to one decimal place, unless otherwise specified.

In general, all eyes of all subjects will be included in analyses, unless otherwise noted. The primary efficacy analysis will be conducted at a significance level of 0.05. Hypothesis testing for the key secondary objectives will be conducted with significance determined at the 0.05 level with multiple testing adjustments (Refer to Section 6.2.1). For most analyses, when a hypothesis test is performed, it will be comparing the ALK-001 and Placebo treatment arms. Confidence intervals will generally be given at a level to mimic the significance level (95% CIs for 0.05 significance level) unless otherwise noted.

Unless otherwise specified, the following treatment arms will generally be included in tables, listings, and figures:

- ALK-001: Subjects randomized to 24 months of ALK-001 at 14 mg per day
- Placebo: Subjects randomized to 24 months of placebo

All analyses will be conducted in SAS®, Version 9.4 or higher (SAS Institute Inc., Cary, NC) or in R, Version 3.6.0 or higher (R Core Team 2019).

4.2. Reference Start Date and Study Day

Reference start date is defined as the date of the first study drug administration following the end of the run-in period, which is designated as Day 1, and the preceding day is Day -1, etc.

Study day will be calculated from the reference start date and will be used to show the start/end day of assessments or events.

Study day will be computed as follows:

- Study Day = Assessment/event date – reference start date + 1 if the assessment/event date is on or after the reference start date.
- Study Day = Assessment/event date – reference start date if the assessment/event date is before the reference start date.

In the situation where the assessment/event date is partial or missing, study day and any corresponding duration will appear as partial or missing in the listings.

4.3. Definition of Baseline

The baseline for efficacy and safety parameters will be defined as the last non-missing assessment obtained prior to the first study drug administration.

4.4. Analysis Visit Window

Unless otherwise specified, the actual scheduled nominal post-baseline visit will be used for by-visit summaries. Post-baseline unscheduled visits and early termination visits will be mapped to a scheduled visit and will only be used in the analysis if the nominal scheduled visit result is missing. Table 1 and Table 2 presents the analysis visit window mapping for unscheduled and early term visits. In the case that multiple unscheduled or early termination visits are in the same analysis window, the one closest to the target date will be used. If multiple assessments are of the same distance from the target day for a particular analysis window, the later assessments will be used.

Table 1: 6-Month Interval Analysis Visit Window for Unscheduled and Early Termination Visits

Analysis Visit	Target Start Day [a]	Analysis Window Study Day [a]	
		Lower	Upper
Month 6	180	91	270
Month 12	360	271	450

Analysis Visit	Target Start Day [a]	Analysis Window Study Day [a]	
		Lower	Upper
Month 18	540	451	630
Month 24	720	631	End of study

[a] Study day will be calculated from the reference start date.

Table 2: 12-Month Interval Analysis Visit Window for Unscheduled and Early Termination Visits

Analysis Visit	Target Start Day [a]	Analysis Window Study Day [a]	
		Lower	Upper
Month 12	360	181	540
Month 24	720	541	End of study

[a] Study day will be calculated from the reference start date.

4.5. Analysis Sets

Analyses are to be performed on the following analysis sets as appropriate. The term 'population' is used interchangeably with 'analysis set'.

- **Screened Set**: All subjects screened.
- **Intent to Treat (ITT) Set**: All randomized subjects. Subjects will be analyzed according to the randomized treatment group.
- **Full Analysis Set (FAS)**: All randomized subjects who have received at least one dose of study drug irrespective of treatment received. In the event that FAS and ITT are identical, only FAS will be used. Subjects will be analyzed according to the randomized treatment group.
- **Per Protocol (PP) Set**: All randomized subjects who have completed the study with no major protocol deviations or problems. Major deviations or problems are those believed to have a material effect on the study outcome measures, including for example early dropouts, pharmacologically significant lapse in treatment, incorrect drug dispensed, test not performed according to manual of performance (MOP), machine or human technical error. The decision as to whether a subject is included in the PP set will be determined by Sponsor and made after blinded review of data and before any unblinded data analysis. Sponsor will generate a list of subjects excluded from PP, and such a list shall be incorporated in the final report.
- **Safety Set**: All subjects who have received at least one dose of study drug irrespective of treatment received. Subjects will be analyzed according to actual treatment received.
- **Pharmacokinetics (PK) Analysis Set**: All subjects who have received at least one dose of study drug and have at least one evaluable PK assessment. Subjects will be analyzed according to actual treatment received.

4.6. Handling of Incomplete/Missing, Unused, and Spurious Data

Missing data, incomplete data, or data not acquired according to the manual of performance, to the extent that it affects the accuracy or reliability of the measurement, will be removed from the presented analysis at the affected timepoints. Data that do not reflect a clinical or physiological phenomenon will be removed from the dataset during blind review.

4.6.1 Imputation Rules for AE Onset Date and Medication Start Date

If the start date (AE onset date, medication start date) is partially missing or completely missing, the following rules will be applied:

- If the start date is completely missing, then the start date will be imputed as the reference start date.
- Partial start date where only the year is known:
  - The start date will be imputed as the reference start date if the year of start date is the same as the year of the reference start date; otherwise, day and month of start date will be imputed as the first day of the year (i.e., 01 January).
- Partial start date where only the month and year are known:
  - The start date will be imputed as the reference start date if the year and month of start date are the same as year and month of the reference start date; otherwise, day of start date will be imputed as the first day of the month.
- If the imputed start date is after the stop/end date, the start date will be imputed as the stop/end date.

4.6.2 Imputation Rules for AE End Date and Medication End Date

If the end date (AE end date, medication end date) is partially missing or completely missing, the following rules will be applied:

- If the end date is completely missing and not ongoing, then the end date will be imputed as the last study participation date.
- Partial end date where only the year is known:
  - The end date will be imputed as the last study participation date if the year of end date is the same as the year of the last study participation date; otherwise, day and month of end date will be imputed as the last day of the year (i.e., 31 December).
- Partial end date where only the month and year are known:
  - The end date will be imputed as the last study participation date if the year and month of end date are the same as year and month of the last study participation date; otherwise, day of end date will be imputed as the last day of the month.
- Imputed stop dates must be on or after the start date.

4.6.3 Missing Severity Assessment for Adverse Events

If the severity is missing for an AE starting on or after the reference start date, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for table summaries, while the actual values will be presented in data listings.

4.6.4 Missing Relationship to Study Drug for Adverse Events

If the relationship to study drug is missing for an AE starting on or after the reference start date, a causality of "Definitely Related" to the study drug will be assigned. The imputed values for relationship to study drug will be used for table summaries, while the actual values will be presented in data listings.

4.6.5 Missing Data Imputations for Sensitivity Analyses of Primary Efficacy Endpoint

The missing values for GA area measurement will be imputed in the following two steps.

Step 1, impute the intermediate missing data to achieve the monotone missing pattern.

The missing value(s) between two visits with measured GA area will be imputed by Markov-Chain Monte-Carlo (MCMC) method, which was proposed by Li (1988) and Liu (1993), to achieve the monotone missing pattern (i.e., where a missing GA area measurement at a visit for a subject implies that GA area measurements at all subsequent visits for that subject are missing). The MCMC model will include treatment arm, the GA area measurements at baseline, Month 6, Month 12, Month 18, and Month 24. This MCMC method will use a seed of 20193001 and a total of 100 imputations are done in the MCMC step.

Step 2, impute the monotone missing data generated in Step 1 using Pattern Mixture Model Method (a copy-reference approach) and Tipping Point Analysis Method (a delta-adjusted approach), respectively.

- Pattern Mixture Model Method (a copy-reference approach):
  - Subjects with monotone missing data in the placebo arm will have missing data imputed based on the observed values in the placebo arm.
  - Subjects in the ALK-001 arm with monotone missing data who did not discontinue treatment or withdraw from the study due to reasons that are potentially related to study drug or lack of efficacy will have missing data imputed based on the observed values in the ALK-001 arm.
  - Subjects in the ALK-001 arm with monotone missing data who discontinued treatment or withdrew from the study due to reasons that are potentially related to study drug or lack of efficacy will have missing data imputed based on placebo arm.

- Tipping Point Analysis Method (a delta-adjusted approach): the tipping point analysis method will be implemented for the ALK-001 arm under the missing not at random (MNAR) assumption by searching for a tipping point that reverses the conclusion regarding positive treatment effect.

- Subjects with monotone missing data in the placebo arm will have missing data imputed based on the observed values in the placebo arm.
- Subjects in the ALK-001 arm with monotone missing data without treatment discontinuation or early withdrawal by subject will have missing data imputed based on the observed values in the ALK-001 arm.
- Subjects in the ALK-001 arm with monotone missing data due to treatment discontinuation or early withdrawal by subject will have missing data imputed based on the available values in the ALK-001 arm (observed values plus values imputed for intermediate missing data) with a shift parameter added to the imputed values.
- Multiple imputation will be implemented with the shift parameter. The shift parameter will be allocated to the missing data point(s) proportionally across timepoints. The precision of the tipping point will be at two decimal points. A tipping point may not exist within reasonable clinical assumptions.

The following three standard step process will be followed to generate inference from the imputed data:

1. Imputation step: the missing data are filled in 100 times to generate 100 complete datasets by either the pattern mixture model method or the tipping point analysis method.
2. Analysis step: the 100 complete datasets are analyzed by using the same approach as for the analysis for the primary objective.
3. Pooling step: the results from the 100 complete datasets are combined for the inference.

4.6.6 Handling of Incorrect MNRead Data

We utilized the MNRead iPad application (app) to improve the testing process for technicians and subjects. Upon test completion, the app automatically computes MNRead parameters. These parameters are then written down on the source documents and entered in the MNRead Case Report Form (CRF) of the Electronic Data Capture (EDC) system. Parameters may also be exported in raw format (CSV) and as an image (JPG) via email.

- **Errors in MNRead Parameters**

  The MNRead app generally provides accurate parameter calculations. However, during blind review, it was found that the app could compute inaccurate parameters, for example in cases where a technician failed to press the "cannot read" button when a subject is unable to see very small letters. This results in incorrect parameters, which should be corrected prior to analysis.

- **Correction of Inaccurate Data**

  To prevent use of erroneous data in the analysis, and prior to database lock (DBL), CSV files received by sponsor prior to DBL will be manually reviewed, marked for errors, and corrected, typically by removing spurious data points. In cases where a CSV file is

unavailable, the data may be re-created from the JPG chart to create a CSV file, if possible. In cases where neither CSV nor JPG files are available, the EDC data will be reviewed and spurious data will be removed.

- **Parameter Calculation Methods**

  MNRead parameters will be calculated using one of the following methods:

  - Manual calculation, similar to traditional paper-based MNRead charts
  - Computer algorithms, such as those provided by the mnreadR package (available at https://cran.r-project.org/web/packages/mnreadR/index.html)

  These steps ensure that the MNRead parameters used in the study are accurate and reliable, maintaining the integrity of the data analysis.

4.7. Derived Variables and Parameters

Variables requiring calculation will be derived using the following formulas:

- Duration of study (month) = (last study participation date – informed consent date +1)/ 30.4375
- Duration of exposure (day) = last treatment date – reference start date +1
- Duration of exposure (month) = duration of exposure (day)/30.4375
- Percentage of duration of exposure (%) is calculated as [total number of days with no lapse in treatment (day)]/ [duration of exposure (day)] x 100.
- Change from baseline = postbaseline value – baseline value
- Percentage change from baseline = ([postbaseline value – baseline value] / baseline value) × 100
- Low Luminance Deficit (LLD) = one eye's Best Corrected Visual Acuity (BCVA) score – Low Luminance Visual Acuity (LLVA) score

5.0. STUDY SUBJECTS

5.1. Subject Disposition

Subject disposition will be summarized for all screened subjects and will include the number of subjects screened, screen failure, randomized, the number and percent of subjects in each analysis set (ITT, FAS, PP, Safety), who have completed and who have prematurely discontinued the study, primary reason for discontinuation (investigator's decision, unmasking, non-compliance, adverse events-related, subject's decision, sponsor's decision, lost to follow-up, death, other).

A flowchart will also be provided with the count of subjects screened, randomized, and who completed the study.

A listing will be provided for all subjects with additional details on the reason for not completing the study, which analysis sets they were in, and reason for excluding from the PP population, if applicable. A listing of screen failure subjects will also be presented.

5.2. Protocol Deviations

Protocol deviations deemed important by Sponsor will be summarized by category (safety, informed consent, eligibility, protocol implementation, and other) and subcategory within category for the ITT Set.

All protocol deviations, including individual subjects when applicable, will be listed.

5.3. Demographic and Baseline Characteristics

Collected demographic and baseline characteristics, including, for example, age at enrollment, sex, race, ethnicity, body weight, height, BMI, age of onset of GA, age of onset of AMD, presence of GA, status of FAF GA in terms of focus/delineation and location within frame, GA foveal status, GA distance to fovea, presence of peripapillary atrophy and contiguity status with GA, GA lesion multifocality status, number of GA lesions, total GA lesion area (mm^2) (FAF), GA FAF junctional zone type and pattern, presence of AMD, presence of intermediate AMD, presence of reticular pseudodrusen(s) (RPD), presence of drusen, presence of large drusen, presence of CNV location and CNV classification, presence of elevated blocked fluorescence on fluorescein angiography (FA), presence of window defect on FA, presence of vascular filling defect on FA, presence of staining on FA, presence of leakage on FA, presence of CNV on FA, presence of chorioretinitis using multi-modal assessment, maximum reading speed by MNRead, reading accessibility index by MNRead, critical print size by MNRead, reading acuity by MNRead, reading speed by IReST, BCVA score, LLVA score, LLD score, FRI index score, TTO, VFQ-25 total score, CNV in the fellow eye collected at baseline, will be summarized by treatment arm for the ITT Set and Safety Set respectively.

A listing of all subjects in the ITT Set with some of their key characteristics will be provided, including for example age at enrollment, age of onset, sex, baseline area of atrophy, visual acuity at baseline.

5.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 22.0 or higher following MedDRA Term Selection Points to Consider.

Medical history will be summarized by system organ class and preferred term by treatment arm for the ITT Set.

A listing of medical history (ocular/non-ocular) for all subjects will be provided, including information on body system, condition/illness/procedure, start and end date, and whether it was ongoing at screening.

5.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary Version September 2023.

Prior medications will be defined as those medications started and ended prior to the reference start date. Concomitant medications will be defined as those medications started on or after the reference start date, or started prior to and continued after the reference start date.

Concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) level 2 and preferred name for the Safety Set. A subject with multiple medications taken within the same ATC level 2 and/or preferred name will be counted only once for that level of summarization.

A listing of concomitant medications for all subjects will be provided, including information on medication/supplement/therapy, indication, dosing information, start and end date, and whether it was taken before or after the reference start date.

6.0. EFFICACY ANALYSIS

Efficacy analysis including primary, key secondary, secondary, and exploratory analysis will be performed primarily using the Full Analysis Set (FAS), with subjects grouped according to the treatment assigned at randomization. Available data from all randomized subjects regardless of adherence to the protocol will be included in the efficacy analyses; this includes data from subjects who discontinued study drug early but continued with study assessments.

Unless otherwise noted, hypothesis testing and estimation of treatment effects will be performed with a mixed effect model that includes data from two treatment arms: ALK-001 and Placebo. All hypothesis tests for efficacy endpoints will be two-sided.

6.1. Analyses of Primary Efficacy Endpoint

An Eligible Eye is defined as an eye with (a) measurable GA and (b) no presence of CNV at baseline as determined centrally by a central reading center according to combined review of optical coherence tomography (OCT) and color fundus photograph (CFP) (“Multimodal imaging”), and FA. GA lesion size will be measured independently by three readers on FAF imaging. The final GA lesion size (area) for each subject’s Eligible Eye, adjudicated from the assessments by three readers, will be used in the analysis.

The primary efficacy endpoint is the mean rate of growth (slope) in the GA area as measured by FAF from baseline to Month 24.

6.1.1 Estimand

The following attributes define the estimand for primary endpoint evaluation:

A. **Treatment**: ALK-001 14 mg versus placebo, taken once a day

B. **Population:** GA subjects defined by inclusion and exclusion criteria in FAS

C. Variable (or endpoint): growth rate (slope) of the GA area over 24 months

D. **Population-level summary:** difference in the mean rate of growth (slope) of the total GA area over 24 months between ALK-001 14 mg versus placebo according to the linear mixed-effects model (LMEM).

E. Intercurrent events (ICEs) and strategies for addressing ICEs:

a. *Treatment changes* (such as interruptions or lapses, non-adherence, dose changes, discontinuation, use of additional therapy due for example to development of CNV): "treatment policy strategy" – i.e., treatment changes will be ignored and all data collected will contribute to the analysis.

b. *Lost to follow-up or withdrawal*: "while on treatment strategy" – i.e., all data collected up to the date a patient has been lost to follow-up or withdrawal will contribute to the analysis.

c. *COVID-19*: "treatment policy strategy" - i.e., impact of COVID-19 pandemic will be ignored and all data collected will contribute to the analysis.

d. *Cataract surgery*: "while on treatment strategy" – i.e., if a patient has cataract surgery in an eye with GA, data collected on that eye up to the time of cataract surgery + 3 months will contribute to the analysis.

These ICEs will be handled with a treatment policy strategy whereby any measured value will be used as is. Missing data resulting from these intercurrent events will be handled implicitly within the linear mixed-effects model analysis that assumes missing at random (MAR).

6.1.2 Hypothesis Testing

The null (H_{1a}) and alternative (H_{1b}) hypotheses for the primary efficacy endpoint are the following:

- H_{1a}: There is no difference between ALK-001 and Placebo in mean growth rate (slope) of the GA area over 24 months based on FAF for the Full Analysis Set.
- H_{1b}: There is difference between ALK-001 and Placebo in mean growth rate (slope) of the GA area over 24 months based on FAF for the Full Analysis Set.

The hypothesis test for the primary endpoint will be based on a two-sided alpha level of 0.05 and the study will be considered positive if the null hypothesis (H_{1a}) is rejected favoring ALK-001.

6.1.3 Main Analysis of Primary Efficacy Endpoint

The mean rates of change (slope) in the GA area will be computed for the ALK-001 and the placebo arms, by use of a linear mixed-effects model applied to the GA area measured on FAF images at time points (baseline, Month 6, Month 12, Month 18 and Month 24) assuming time as continuous and linear ("slope model").

The analysis model will use the change from baseline in the GA area measured by FAF as the response variable, and will include treatment arm (ALK-001, placebo), pattern of FAF at the junctional zone of GA (banded/diffuse, focal/other/cannot grade), GA lesion multifocality (multifocal, unifocal/other/cannot grade) and foveal status (foveal sparing, subfoveal/cannot grade) as fixed effects, baseline GA lesion area and time (year, continuous assuming linearity) as

covariates, time × treatment interaction, and baseline GA lesion area × time interaction. Random effects include subject and subject's eye (OD or OS). A common unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger's (Kenward and Roger 1997) method will be used to estimate denominator degrees of freedom. If the model fails to converge, alternative structures (heterogenous autoregressive (1), heterogeneous compound symmetry, autoregressive (1), or compound symmetry, in this order) will be considered.

The mean rate of change (mm^2/year), standard error, and 95% confidence interval (CI) will be estimated from baseline to Month 24 for each treatment arm. The estimated difference in slopes among the treatment groups along with the 95% CIs and p-value will be provided to test the significance of the treatment effect.

The observed values for the GA area (mm^2) of Eligible Eyes will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The mean change from baseline ± the standard error in the GA area (mm^2) of Eligible Eyes as well as the Least-Squares (LS) mean of the change from baseline ± the standard error in GA area (mm^2) of Eligible Eyes will be plotted over time by treatment group.

6.1.4 Piecewise Analysis

The mean rate of change in the GA area will be compared between the ALK-001 arm and the Placebo arm by use of a piecewise linear mixed-effects model assuming time as continuous and piecewise linear ("piecewise slope model").

The analysis to be performed will be similar to what is described in Section 6.1.3 except that a breakpoint (knot) at Month 12 visit will be added which allows for the slope of lesion growth to differ between the period of baseline to Month 12 and the period of Month 12 to Month 24 for each treatment group. The mean rate of change (mm^2/year) for baseline to Month 12 and for Month 12 to Month 24, their associated standard error, and 95% CI will be estimated for each treatment arm. The estimated difference in slopes for baseline to Month 12 and for Month 12 to Month 24 among the treatment groups along with the 95% CIs and p-value will be provided.

Similarly, a breakpoint (knot) at Month 6 will be added, and similar outputs for Month 6 to Month 24 will be provided.

6.1.5 Sensitivity Analyses of Primary Efficacy Endpoint

Sensitivity analyses will be performed to evaluate the robustness of the primary analysis results as further described in this section.

6.1.5.1. Missing Data Analyses Based on Multiple Imputation

- The missing data of the GA area are filled in 100 times to generate 100 complete datasets by the pattern mixture model method and the tipping point analysis method, respectively, as described in Section 4.6.5.

- The 100 complete datasets, imputed by either the pattern mixture model method or the tipping point analysis method, are analyzed by using the same approach as for the primary analysis for the primary efficacy endpoint in Section 6.1.3.
- The results from the 100 complete datasets are combined to generate the estimates as described in Section 6.1.3.

6.1.5.2. Per Protocol Set

The main analysis described in Section 6.1.3 will be repeated using the PP Set to investigate the impact of changing the population on the estimand.

The summary and presentation of the observed values for the total area of GA lesion(s) by treatment group and visit described in Section 6.1.3 will be repeated using the PP Set.

6.1.5.3. Other Sensitivity Analyses

The main analysis described in Section 6.1.3 will be repeated with the following modifications:

- **Square root of the GA lesion area**: using the change from baseline in the square root of the GA lesion area instead of the change from baseline in the GA lesion area as response variable and replacing baseline GA lesion area by square root of baseline GA lesion area in the model.
- **Restriction on baseline area**: subject eyes are included only if GA lesion at baseline exceeds 0.5 mm^2.
- **Only first 12 months**: excluding all data points after the 12-month visit.
- **Absolute change at Month 24**: using change from baseline in GA lesion area as response variable, assuming time as categorical, for both the GA area and the square root of GA area. Replacing baseline GA lesion area by square root of baseline GA lesion area in the model for analysis of the square root of GA area.

  The LS mean of the change from baseline in GA area (mm^2) of Eligible Eyes ± the standard error will be plotted over time by treatment group, assuming time as categorical.
- **Percentage change at Month 24**: using percentage change from baseline in GA lesion area as response variable, assuming time as categorical, for both the GA area and the square root of GA area. Replacing baseline GA lesion area by square root of baseline GA lesion area in the model for analysis of the square root of GA area.
- **Exclusion of eyes with CNV at baseline or historical determined by PI:** Eligible Eye(s) reported to have CNV at baseline or in medical history will be excluded from the analysis.

6.1.6 Subgroup Analyses of Primary Efficacy Endpoint

Subgroup analyses will be performed to evaluate the consistency of the primary analysis results across subgroups defined by demographic and baseline characteristics. The main analysis described in Section 6.1.3 will be repeated for the primary efficacy endpoint for each of the following subgroups:

- **Age group:** <75 years, ≥75 years at enrollment
- **Sex:** male, female
- **Baseline BCVA**: BCVA 64 letters (~20/50) or better, BCVA less than 64 letters
- **Baseline LLD**: LLD 30 letters or more, LLD less than 30 letters
- **Baseline GA lesion size**: small (< 7.5 mm^2), large (>= 7.5 mm^2)
- **Baseline GA lesion multifocality:** multifocal, unifocal
- **Baseline GA lesion foveal status:** foveal sparing, subfoveal

Forest plot will be produced for mean rate of change (mm^2/year) or slope of total GA area (mm^2) from the baseline to Month 24 for each treatment arm, difference in mean rate of change and associated 95% CI for overall population and by subgroups.

6.2. Analyses of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are listed in Section 2.2.2. Formal hypothesis testing for key secondary endpoints, evaluated based on data from baseline to Month 24 for LLVA and BCVA, will be performed.

Hypothesis testing for two key secondary efficacy endpoints will be performed in the manner specified in Section 6.2.1.

6.2.1 Hypotheses Testing and Type I Error Management

If the hypothesis test for the primary endpoint is statistically significant favoring ALK-001, then hypotheses testing will be performed for the key secondary endpoints. The null (H_{2a}, H_{3a}) and alternative (H_{2b}, H_{3b}) hypotheses for the key secondary efficacy endpoints are the following:

- $H2_a$: There is no difference between ALK-001 and Placebo regarding mean change from baseline in LLVA score at Month 24, as assessed by an ETDRS chart or an EVA system.
- $H2_b$: There is difference between ALK-001 and Placebo regarding mean change from baseline in LLVA score at Month 24, as assessed by an ETDRS chart or an EVA system.
- $H3_a$: There is no difference between ALK-001 and Placebo regarding mean change from baseline in BCVA score at Month 24, as assessed by an ETDRS chart or an EVA system.
- $H3_b$: There is difference between ALK-001 and Placebo regarding mean change from baseline in BCVA score at Month 24, as assessed by an ETDRS chart or an EVA system.

To control type I error, hypotheses for the key secondary efficacy endpoints will be tested in a fixed sequencing order, first for H_{2a}, followed by H_{3a}, based on a two-sided alpha level of 0.05. Sequential testing will continue as long as all preceding hypotheses can successfully be rejected at alpha level of 0.05 favoring ALK-001.

6.2.2 Low Luminance Visual Acuity (LLVA)

LLVA is measured using a letter score in an equivalent manner by either an ETDRS chart or an EVA system for each eye at visits V01 (Screening), V04 (Month 6), V06 (Month 12), V08 (Month 18), and V10 (Month 24).

The LLVA score at time points (baseline, Month 6, Month 12, Month 18 and Month 24) from Eligible Eyes will be summarized and analyzed using mixed effect model for repeated measure (MMRM). The analysis model will use change from baseline in LLVA score as the response variable, and will include treatment arm (ALK-001, placebo), pattern of FAF at the junctional zone of GA (banded/diffuse, focal/other/cannot grade), GA lesion multifocality (multifocal, unifocal/other/cannot grade), foveal status (foveal sparing, subfoveal/cannot grade) and time (year, categorical) as fixed effects, baseline GA lesion area and baseline LLVA score as covariates, time (year, categorical) × treatment and baseline LLVA score × time (year, categorical) interaction terms, subject and subject's eye (OD or OS) as random effects. A common unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger's (Kenward and Roger 1997) method will be used to estimate denominator degrees of freedom. If the model fails to converge, alternative structures (heterogenous autoregressive (1), heterogeneous compound symmetry, autoregressive (1), or compound symmetry, in this order) will be considered.

The LS mean of the change from baseline in LLVA score of Eligible Eyes, standard error, and 95% confidence interval (CI) will be estimated from baseline to Month 24 for each treatment arm. The estimated difference in change from baseline among the treatment groups along with the 95% CIs and p-value will be provided to test the significance of the treatment effect.

The observed values for LLVA score of Eligible Eyes will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The mean change from baseline in LLVA score of Eligible Eyes ± the standard error as well as the LS mean of the change from baseline in LLVA score of Eligible Eyes ± the standard error will be plotted over time by treatment group.

The categorical changes (a decrease of greater than 15, a decrease greater than 7 to 15, little change from baseline [≤ 7], an increase of greater than 7 to 15, and an increase of greater than 15) for Eligible Eyes will be summarized by treatment group and visit.

6.2.3 Best Corrected Visual Acuity (BCVA)

BCVA is measured using a letter score in an equivalent manner by either an ETDRS chart or an EVA system for each eye at visits V01 (Screening), V04 (Month 6), V06 (Month 12), V08 (Month 18), and V10 (Month 24).

An analysis that mirrors that of LLVA in Section 6.2.2 will be repeated for BCVA.

6.3. Analyses of Secondary Efficacy Endpoints

All secondary efficacy analyses will be performed using the Full Analysis Set (FAS) unless otherwise noted.

6.3.1 Low Luminance Deficit (LLD)

The low luminance deficit (LLD) score is computed as the difference between one eye's BCVA and LLVA scores.

The LLD score at time points (baseline, Month 6, Month 12, Month 18 and Month 24) from Eligible Eyes will be summarized and analyzed in a similar way using MMRM described in Section 6.2.2. The analysis model will use change from baseline in LLD score as the response variable, and will include treatment arm (ALK-001, placebo), pattern of FAF at the junctional zone of GA (banded/diffuse, focal/other/cannot grade), GA lesion multifocality (multifocal, unifocal/other/cannot grade), foveal status (foveal sparing, subfoveal/cannot grade) and time (year, categorical) as fixed effects, baseline GA lesion area and baseline LLD score as covariates, time (year, categorical) × treatment and baseline LLD score × time (year, categorical) interaction terms, subject and subject's eye (OD or OS) as random effects. A common unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger's (Kenward and Roger 1997) method will be used to estimate denominator degrees of freedom. If the model fails to converge, alternative structures (heterogenous autoregressive (1), heterogeneous compound symmetry, autoregressive (1), or compound symmetry, in this order) will be considered.

The LS mean of the change from baseline in LLD score of Eligible Eyes, standard error, and 95% confidence interval (CI) will be estimated from baseline to Month 24 for each treatment arm. The estimated difference in change from baseline among the treatment groups along with the 95% CIs and p-value will be provided to test the significance of the treatment effect.

The observed values for LLD score of Eligible Eyes will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The mean change from baseline in LLD score of Eligible Eyes ± the standard error as well as the LS mean of the change from baseline in LLD score of Eligible Eyes ± the standard error will be plotted over time by treatment group.

6.3.2 Maximum Reading Speed by MNRead

MNRead measures reading speed for each eye at visits V01 (Screening), V04 (Month 6), V06 (Month 12), V08 (Month 18), and V10 (Month 24).

Maximum reading speed (MRS) by MNRead at time points (baseline, Month 6, Month 12, Month 18 and Month 24) from Eligible Eyes and MRS greater than zero at baseline, will be summarized and analyzed in a similar way using MMRM described in Section 6.2.2. The analysis model will use change from baseline in maximum reading by MNRead as the response variable, and will include treatment arm (ALK-001, placebo), pattern of FAF at the junctional zone of GA (banded/diffuse, focal/other/cannot grade), GA lesion multifocality (multifocal, unifocal/other/cannot grade), foveal status (foveal sparing, subfoveal/cannot grade) and time (year, categorical) as fixed effects, baseline GA lesion area and baseline maximum reading speed as covariates, time (year, categorical) × treatment and baseline maximum reading speed × time (year, categorical) interaction terms, subject and subject's eye (OD or OS) as random effects. A common unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger's (Kenward and Roger 1997) method will be used to estimate denominator

degrees of freedom. If the model fails to converge, alternative structures (heterogenous autoregressive (1), heterogeneous compound symmetry, autoregressive (1), or compound symmetry, in this order) will be considered.

The LS mean of the change from baseline in the maximum reading speed of Eligible Eyes, standard error, and 95% confidence interval (CI) will be estimated from baseline to Month 24 for each treatment arm. The estimated difference in change from baseline among the treatment groups along with the 95% CIs and p-value will be provided to test the significance of the treatment effect.

The observed values for the maximum reading speed of Eligible Eyes will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The mean change from baseline in the maximum reading speed of Eligible Eyes ± the standard error, as well as the LS mean of the change from baseline in the maximum reading speed of Eligible Eyes ± the standard error will be plotted over time by treatment group.

The categorical changes (improvements of ≥ 20 to <40, ≥ 40 to <60, ≥ 60 and minimal/no change (-20 to 20), worsening of ≥ 20 to <40, ≥ 40 to <60, ≥ 60) for Eligible Eyes will be summarized by treatment group and visit.

6.3.3 Binocular Reading Speed by IReST

Binocular reading speed, measured as correctly read words per minute, assessed by IReST is performed at visits V01 (Screening), V04 (Month 6), V06 (Month 12), V08 (Month 18), and V10 (Month 24).

Binocular reading speed by IReST at time points (baseline, Month 6, Month 12, Month 18 and Month 24) will be summarized and analyzed in a similar way using MMRM described in Section 6.2.2. The analysis model will use change from baseline in binocular reading speed by IReST as the response variable, and will include treatment arm (ALK-001, placebo), pattern of FAF at the junctional zone of GA (banded/diffuse, focal/other/cannot grade), GA lesion multifocality (multifocal, unifocal/other/cannot grade), foveal status (foveal sparing, subfoveal/cannot grade) and time (year, categorical) as fixed effects, baseline GA lesion area and baseline binocular reading speed as covariates, time (year, categorical) × treatment and baseline binocular reading speed × time (year, categorical) interaction terms, subject as a random effect. A common unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger's (Kenward and Roger 1997) method will be used to estimate denominator degrees of freedom. If the model fails to converge, alternative structures (heterogenous autoregressive (1), heterogeneous compound symmetry, autoregressive (1), or compound symmetry, in this order) will be considered.

The LS mean of the change from baseline in the binocular reading speed, standard error, and 95% confidence interval (CI) will be estimated from baseline to Month 24 for each treatment arm. The estimated difference in change from baseline among the treatment groups along with the 95% CIs and p-value will be provided.

The observed values for the binocular reading speed will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The mean change from baseline in the binocular reading speed ± the standard error as well as the LS mean of the change from baseline in the binocular reading speed ± the standard error will be plotted over time by treatment group.

6.3.4 Visual function questionnaires

Visual function questionnaires are performed at visits V01 (Screening) or V02 (Day 1), V06 (Month 12), and V10 (Month 24).

6.3.4.1. Functional Reading Independence (FRI) Index Score

The FRI index score will be calculated per the scoring algorithm in the FRI Index user's manual.

FRI index score at time points (baseline, Month 12 and Month 24) will be summarized and analyzed in a similar way using MMRM described in Section 6.2.2. The analysis model will use change from baseline in FRI index score as the response variable, and will include treatment arm (ALK-001, placebo), pattern of FAF at the junctional zone of GA (banded/diffuse, focal/other/cannot grade), GA lesion multifocality (multifocal, unifocal/other/cannot grade), foveal status (foveal sparing, subfoveal/cannot grade) and time (year, categorical) as fixed effects, baseline GA lesion area and baseline FRI index score as covariates, time (year, categorical) × treatment and baseline FRI index score × time (year, categorical) interaction terms, subject as a random effect. A common unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger's (Kenward and Roger 1997) method will be used to estimate denominator degrees of freedom. If the model fails to converge, alternative structures (heterogenous autoregressive (1), heterogeneous compound symmetry, autoregressive (1), or compound symmetry, in this order) will be considered.

The LS mean of the change from baseline in FRI index score, standard error, and 95% confidence interval (CI) will be estimated from baseline to Month 24 for each treatment arm. The estimated difference in change from baseline among the treatment groups along with the 95% CIs and p-value will be provided.

The observed values for FRI index score will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

6.3.4.2. Visual Functioning Questionnaire 25 Item Version (VFQ-25)

The VFQ-25 total score will be calculated per the scoring algorithm in the user's manual.

VFQ-25 total score at time points (baseline, Month 12 and Month 24) will be summarized and analyzed in a similar way using MMRM described in Section 6.2.2. The analysis model will use change from baseline in VFQ-25 total score as the response variable, and will include treatment arm (ALK-001, placebo), pattern of FAF at the junctional zone of GA (banded/diffuse, focal/other/cannot grade), GA lesion multifocality (multifocal, unifocal/other/cannot grade), foveal status (foveal sparing, subfoveal/cannot grade) and time (year, categorical) as fixed effects, baseline GA lesion area and baseline VFQ-25 total score as covariates, time (year, categorical) × treatment and baseline VFQ-25 total score × time (year, categorical) interaction terms, subject as a random effect. A common unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger's (Kenward and Roger 1997) method will be used to

estimate denominator degrees of freedom. If the model fails to converge, alternative structures (heterogenous autoregressive (1), heterogeneous compound symmetry, autoregressive (1), or compound symmetry, in this order) will be considered.

The LS mean of the change from baseline in the VFQ-25 total score, standard error, and 95% confidence interval (CI) will be estimated from baseline to Month 24 for each treatment arm. The estimated difference in change from baseline among the treatment groups along with the 95% CIs and p-value will be provided.

The observed values for the VFQ-25 total score will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

6.3.4.3. Time Trade-Off (TTO) Questionnaire

Descriptive statistics for values and changes from baseline for time trade-off questionnaires will be summarized by treatment arm and visit.

6.3.4.4. Open-Ended Questionnaire

A listing of all answers on a per question per subject basis will be provided.

6.3.5 Incidence of CNV in the Study Eye

The number and percentage of subjects with incidence of CNV in the study eye, when the fellow eye has CNV at baseline, and 95% exact CI will be generated for each treatment arm. The proportion difference among the treatment groups, and the associated 95% Wald CI and Fisher's exact test p-value will also be provided.

6.4. Exploratory Efficacy Analyses

Descriptive statistics for values and changes from baseline for the continuous endpoints will be summarized by treatment arm and visit, and count and percentage for the categorical endpoints will be summarized by treatment arm.

- Changes in retinal sensitivity as measured by fundus-tracking microperimetry
- Incidence of CNV in the study eye, when the fellow eye has intermediate AMD at baseline
- Incidence of advanced AMD (CNV or GA) in the fellow eye, when the fellow eye has intermediate AMD at baseline

7.0. SAFETY ANALYSIS

Safety and tolerability are evaluated by AEs, SAEs, clinical laboratory test results, body weight, vital signs, 12-lead ECG findings, physical examination, and ocular exam and intraocular pressure (IOP). All analyses of the safety data are performed using the Safety Set. Descriptive statistics are presented by treatment group in the Safety Set. No formal statistical testing is performed for safety analyses.

7.1. Treatment Exposure and Compliance

Treatment exposure and compliance will be summarized by treatment arm, including the following:

- Duration of exposure (month), including number and percent of subjects with duration of exposure: < 1 month, >= 1 month, >= 3 months, >= 6 months, >= 12 months, >= 18 months
- Percentage of duration of exposure (%)
- Treatment compliance at Month 6, Month 12, Month 18 and Month 24, including numeric descriptive statistics and number and percent of subjects with compliance: < 70%, 70 - 90%, >90%

The treatment exposure and compliance data will be listed.

7.2. Adverse Events and Serious Adverse events

All reported adverse events (AEs) will be coded using MedDRA version 22.0 or higher following the MedDRA Term Selections Points to Consider.

An AE will be considered a treatment-emergent adverse event (TEAE) if it starts on or after the reference start date or if it starts before the reference start date but worsens on or after the reference start date, up to 28 days after last study drug administration.

The overall summary of TEAEs by treatment arm will include the numbers and percentages of subjects with at least one TEAE in the following categories:

- Any TEAE
- TEAE by Maximum Severity (evaluated by the investigator as Mild, Moderate and Severe)
- TEAE related to study drug (evaluated by the investigator as definitely, possibly, probably related)
- Treatment-emergent SAE
- Treatment-emergent SAE related to study drug (evaluated by the investigator as definitely, possibly, probably related)
- TEAE leading to study drug discontinuation
- TEAE leading to study drug interruption
- TEAE leading to study discontinuation
- TEAE leading to death (outcome = “Fatal”)

In addition, the numbers and percentages of subjects with at least one TEAE will be summarized by system organ class (SOC) and preferred term (PT) for the following categories:

- Any TEAE

- TEAE by Maximum Severity (evaluated by the investigator as Mild, Moderate, and Severe)
- TEAE related to study drug (evaluated by the investigator as definitely, possibly, probably related)
- Treatment-emergent SAE
- Treatment-emergent SAE related to study drug (evaluated by the investigator as definitely, possibly, probably related)
- TEAE leading to study drug discontinuation
- TEAE leading to study drug interruption
- TEAE leading to study discontinuation
- TEAE leading to death (outcome = "Fatal")

Subjects who experienced multiple AEs within the same SOC or PT will only be counted once for that SOC or PT for that level of summarization. The maximum severity will be used in the summary of "TEAE by maximum severity" for subjects who experienced multiple AEs within the same SOC/PT.

Common TEAEs with at least 5% subjects in treatment group ALK-001 or with at least 2% subjects in treatment group ALK-001 and greater than placebo in percentage, will be summarized by PT respectively.

For each preferred term (PT), the number and percentage of subjects experiencing the event will be summarized by treatment arm and by duration of treatment at the time of first occurrence (categorized as <6 months, 6 – 12 months, >12 – 18 months, and >18 months). An estimated value and 95% confidence interval will be presented for the true rate of at least one AE or SAE by treatment arm.

Listings by subject will be provided for all AEs, SAEs, AEs leading to study discontinuation, and AEs leading to death, respectively.

7.3. Laboratory Tests

Laboratory tests, including laboratory parameters in chemistry, hematology, and lipids panel, are required at V01 (Screening), V04 (Month 6), V06 (Month 12), V08 (Month 18), V10 (Month 24), optional at all other visits.

Descriptive statistics for values and changes from baseline for laboratory results will be summarized by treatment arm and visit for chemistry, hematology, and lipids panel parameters listed in Appendix 2.

The numbers and percentages of subjects for each laboratory parameter with quantitative laboratory values categorized as low, normal, and high, will be summarized by treatment arm and visit. Shift table in laboratory results (low/normal/high) from baseline to each post-baseline visit for each laboratory parameter will also be presented.

In accordance with the FDA guideline on Drug-Induced Liver Injury (*Drug-Induced Liver Injury: Premarketing Clinical Evaluation (2009) Section E2*)), following occurrences will be summarized by treatment arm and visit:

- Elevations greater than 3, 5, 10, and 20 times the upper limit of normal for AST, ALT, and either AST or ALT
- Elevations of bilirubin greater than 2 times the upper limit of normal
- Elevations of alkaline phosphatase greater than 1.5 times the upper limit of normal
- Elevations of ALT or AST greater than 3 times the upper limit of normal accompanied by elevations of bilirubin greater than 1.5 or 2 times the upper limit of normal.

The mean change from baseline ± the standard error for laboratory parameters: ALT, AST, total bilirubin, triglycerides, HDL and LDL, will be plotted over time by treatment group.

All laboratory data will be listed.

There will be no imputation for missing laboratory results. For quantitative laboratory results reported as '<X' or '≤X' or '>X' or '≥X', a value of X will be used in the summary tables. The actual results as collected will be displayed in the listings.

7.4. Vital Signs

Vital signs collected include BMI (calculated from weight and height), body temperature, respiratory rate, heart rate, and blood pressure (systolic and diastolic), are required at V01 (Screening), V02 (Randomization / Day 1), V04 (Month 6), V06 (Month 12), V08 (Month 18) and V10 (Month 24), optional at V03 (Month 3),V05 (Month 9) and V07 (Month 15), V09 (Month 21).

Descriptive statistics for values and changes from baseline for each vital sign parameter will be summarized treatment arm and visit.

All vital sign results will be listed.

7.5. 12-Lead ECG

ECG measurements, including QT interval corrected by the Fridericia's formula (QTcF) and interpretation of ECG results (normal, abnormal not clinically significant, abnormal clinically significant), are required at V01 (screening), V06 (Month 12) and V10 (Month 24), optional at V05 (Month 9) and V07 (Month 15).

Descriptive statistics for values and changes from baseline for QTcF will be summarized by treatment arm and visit.

The numbers and percentages of subjects will be summarized by treatment arm and visit for QTcF >450, >480 and > 500 msec and for QTcF change from baseline >30 and > 60 msec, respectively.

The numbers and percentages of subjects whose ECG interpretations by the investigator were normal, abnormal not clinically significant, and abnormal clinically significant will be summarized by treatment arm and visit.

All ECG results will be listed.

7.6. Physical Exam

A physical exam is conducted (sometimes optional) at visits V01 (Screening), V04 (Month 6), V06 (Month 12), V08 (Month 18) and V10 (Month 24). Results of the physical exam are considered normal, abnormal not clinically significant, or abnormal clinically significant.

A listing of all physical exam results will be provided.

7.7. Ocular Examinations and Intraocular Pressure

An ocular exam is performed (sometimes optional) at V01 (Screening), V04 (Month 6), V06 (Month 12), V08 (Month 18) and V10 (Month 24), as clinically indicated or based on routine care. Results of the ocular exam are either marked as (a) consistent with GA or (b) present with an abnormality that is inconsistent with GA, as assessed by the investigator. For cases where an abnormality inconsistent with GA was noted, clinical significance is evaluated by investigator.

Descriptive statistics for values and changes from baseline for intraocular pressure (IOP) by OD and OS will be summarized by treatment arm and visit.

The numbers and percentages of subjects whose ocular examination findings by the investigator were normal, abnormal not clinically significant, and abnormal clinically significant will be summarized by treatment arm and visit.

A listing of ocular examinations will be provided, including results marked inconsistent with GA and their clinical significance.

8.0. PHARMACOKINETIC ANALYSIS

Pharmacokinetics of ALK-001 over time when administered daily for 24 months will combine measures of absolute concentrations and percentage replacement with deuterated forms of vitamin A (as the sum of retinol and retinyl palmitate), retinol, and retinyl palmitate in plasma (required at all in-person visits except V02).

Pharmacokinetic measures include the following:

- Deuterated retinol as a fraction of total retinol
- Deuterated retinyl palmitate as a fraction of total retinyl palmitate
- Deuterated vitamin A as a fraction of total vitamin A, where vitamin A is computed as the sum of retinol and retinyl palmitate
- Other tested deuterated vitamin A metabolite(s) as a fraction of total vitamin A metabolite(s)
- Absolute concentrations (ng/mL) for each of the above analytes

Descriptive statistics for values and changes from baseline will be summarized for pharmacokinetic measures by treatment arm and visit (where a blood sample collection is performed).

The mean for pharmacokinetic parameters ± the standard error will be plotted over time by treatment group.

The following method will be used to handle measurements that are below quantification limits (BQL):

- For subjects randomized to ALK-001:
    - At V01 (Screening) or V02 (Day 1), BQL deuterated values will be set to 0 and non-deuterated values will be set to the lower limit of quantification (LLOQ).
    - At visits other than V01 (Screening) or V02 (Day 1), all BQL values will be set to LLOQ.
- For subjects randomized to placebo:
    - BQL deuterated values will be set to 0 and BQL non-deuterated values will be set to LLOQ.

All PK analyses will be conducted in the PK Analysis Set using the above methods, on values provided by the lab while handling BQL values mentioned above, as well as on extrapolated values.

A listing of pharmacokinetic measures will be provided.

9.0. INTERIM ANALYSIS

No interim safety/efficacy analysis was planned or performed in the study.

10.0. REFERENCES

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Appendix 1: Assessments and Visit Schedule

Period		Screening/Baseline and Run-In[15] Period		Initial Treatment Period																	
Study Months (m)		between approx. 20 and 40 days before day 1	Day 1 Start of Treatment	Day 2-3 mo	3 mo	3-6 mo	6 mo	6-9 mo	9 mo	9-12 mo	12 mo	12-15 mo	15 mo	15-18 mo	18 mo	18-21 mo	21 mo	21-24 mo	24 mo End of Study	Early Termination[13]
Visit Window				monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]	monthly	±5 days[11]		
Visit (V) #	Standard of Care CPT Code	V01 Screening start Run-in[15] period starts	V02 Screening end/ Baseline/ Randomization	Phone Follow-up	V03	Phone Follow-up	V04	Phone Follow-up	V05[12] (Optional)	Phone Follow-up	V06	Phone Follow-up	V07[12] (Optional)	Phone Follow-up	V08	Phone Follow-up	V09[12] (Optional)	Phone Follow-up	V10	ET (Early Termination)
Screening Period																				
Informed Consent	-	●																		
Size 0 Capsule Swallow Test	-	O																		
Demographics	-	●																		
Clinical Diagnosis	-	●																		
Medical, Surgical, and Ocular History	-	●																		
Collection of Historical Retinal Images	-	●																		
Vitamin A information, counseling & quiz[8]	-	●																		
Eligibility (Inclusion/Exclusion) Criteria	-	●	●																	
General Health																				
Prior and concomitant medications	-	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Treatment Emergent Adverse Events (AE) and SAEs	-			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Check-up phone calls	-			●		●		●		●		●		●		●		●		
Study Drug Reconciliation	-				●		●		O[12]		●		O[12]		●		O[12]		●	●
Vital signs	-	●	●		●		●		O[12]		●		O[12]		●		O[12]		●	●
12-Lead ECG	93005	●									●								●	O[13]
Physical Exam or Assessment[1]	99396	C					ACI / RC				● RC				ACI / RC				● RC	O[13]
Eye Exam[2]	92014	●					ACI / RC				● RC				ACI / RC				● RC	O[13]
Quality of Life and Visual Function																				
Visual Acuity (ETDRS-BCVA)[2]	92015	●	●				●				●				●				●	O[13]
Low Luminance Visual Acuity (LLVA)[2]	99173	●	●				●				●				●				●	O[13]
Reading Speed (IReST, MNREAD)[2]	-	●	●				●				●				●				●	O[13]
Vision Questionnaires (VF14, FRI)	-	●					●				●				●				●	O[13]
Ocular Imaging																				
Color Fundus Photograph (CFP)[2]	92250	●					ACI / RC				● RC				ACI / RC				● RC	O[13]
OCT Angiography (OCTA) or Fluorescein Angiogram (FA)[2]	92134 or 92235	●					● RC				● RC				● RC				● RC	ACI/RC
Fundus Autofluorescence (FAF)[2]	92250	●	● if screening older than 1 mo.				● RC				● RC				● RC				● RC	O[13]
Spectral Domain OCT (SD-OCT)[2]	92134	●					● RC				● RC				● RC				● RC	O[13]
Treatment																				
Treatment of CNV[16]	67028	ACI / RC	ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC		ACI / RC	ACI / RC
Psychophysical function																				
Microperimetry[2]	92083	●	●				● RC				● RC				● RC				● RC	O[13]
Clinical Laboratory (Central Lab)																				
Biochemistry[3]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Hematology[4]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Lipids[5]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Glucose[14]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Vitamin A and Pharmacokinetics (PK)[6]	-	●			O[12]		●		O[12]		●		O[12]		●		O[12]		●	●
Complement[17]	-	See footnotes																	O	O[13]
Genotype[17]	-	See footnotes																		
Pregnancy Test[7]	-	O																		
Miscellaneous																				
Randomization	-		●																	
Drug Dispensing[9]	-	● Placebo	●		●		●		●		●		●		●		●			

● : Protocol Procedure O : Optional ACI/RC: Perform As Clinically Indicated or for Routine Care

1 Comprehensive physical exam (C) or simplified physical exam (S) when performed by PI or delegated personnel; Limited physical assessments when performed off-site by a home nurse.
2 Both eyes.
3 Biochemistry (CMP panel, fasting): Sodium, Potassium, Chloride, Bicarbonate, Urea, Creatinine, Calcium, Total Protein, Bilirubin, Albumin, Alkaline phosphatase, AST, ALT
4 Hematology (differential, fasting): WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, RBC, HGB, HCT, MCV, MCH, PLT
5 Lipids (fasting): total cholesterol, triglycerides, HDL, LDL
6 Collect approx. 6 mL of blood, extract plasma (~ 2 x 1.5 mL), store at below -20°C in provided glass vials, ship in bulk upon request by sponsor.
7 Optional. As determined by the PI.
8 Self-administered short quiz to ensure subject understands the instructions
9 Investigator may dispense the appropriate number of bottles until the next visit (usually 3 or 6 bottles). At screening, a bottle containing placebo is dispensed to check subject's proper compliance at V02. Check numeral 15.
10 This final, exit visit shall occur 3 months after permanent discontinuation of the study drug or completion of the treatment period
11 Reasonable exceptions may be granted by sponsor if such exception would not be expected to influence data collection or continuous treatment of the study subject
12 Optional procedures performed if visit is done in person. Upon investigator's decision and if the subject does not have ongoing adverse events that are possibly associated with the study drug, this visit can be replaced by a phone call. Study drug is then directly shipped to the subject and in person assessments are not performed.
13 Perform optional procedures only if the early termination visit occurs at least 3 months following one of the major visits (in grey background): V04, V06, V08 and V10. Ask sponsor if unsure.
14 Glucose (fasting): HbA1C
15 Run-In period: all screen subjects may start receiving placebo for approximately 4 weeks to measure compliance. Only those subjects with greater than 80% adherence during the run-in period will be randomized
16 Proceed according to the PI's standard of care.
17 Genotype and complement can be measured at any time during the study upon sponsor's request. This will be done through central labs.

Appendix 2: Laboratory Tests for Chemistry, Hematology and Lipid Panel

<table>
<tr>
<td rowspan="2">Chemistry:
• Alkaline phosphatase
• Alanine aminotransferase (ALT)
• Aspartate aminotransferase (AST)
• Total Bilirubin
• Blood urea nitrogen (BUN)
• Creatinine
• eGFR (CKD-EPI)
• Glucose
• Calcium
• Protein - total
• Albumin
• Sodium
• Potassium
• Chloride
• Bicarbonate</td>
<td>Hematology:
• Hemoglobin
• Hematocrit
• Red blood cells (RBC)
• White blood cells (WBC)
• Neutrophils (absolute, %)
• Lymphocytes (absolute, %)
• Monocytes (absolute, %)
• Eosinophils (absolute, %)
• Basophils (absolute, %)
• MCV
• MCH
• Platelet count</td>
</tr>
<tr>
<td>Lipid Panel:
• Total Cholesterol
• Triglycerides
• HDL
• LDL</td>
</tr>
</table>

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